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Canadian Adverse Drug Reaction Newsletter

Therapeutic Products Programme

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Update on calcium-channel blockers

The Therapeutic Products Directorate recently undertook a comprehensive review of the safety of calcium-channel blockers (CCBs), with advice obtained from an independent Ad Hoc Expert Advisory Committee (EAC) convened especially to assist in this review.

As a result of this review, a "Dear Doctor Letter" was issued on June 25, 1997, which reemphasized the approved uses of CCBs in Canada. It affirmed that immediate-release nifedipine capsules are not indicated in the management of essential hypertension and that CCB preparations, when approved for the treatment of hypertension in Canada, are limited to second-line therapy after diuretics and/or •-blockers, for which beneficial clinical outcome data exist. CCBs are not indicated for the treatment of congestive

heart failure or unstable angina, or immediately following myocardial infarction.

Use of immediate-release nifedipine capsules is not recommended for the acute reduction of blood pressure. When used in this way, the time course and magnitude of blood pressure response is unpredictable. Serious adverse events, including myocardial infarction, stroke and death, have occurred in this setting.<1>

Furthermore, attention should be drawn to the route of biotransformation of CCB preparations, namely by the cytochrome-P-450 system. This is particularly relevant for dihydropyridine CCBs, such as nifedipine, nicardipine and felodipine, which are metabolized primarily by the CYP 3A4 isoenzyme and which may therefore interact significantly with other compounds that are metabolized by this same enzyme or that affect its activity. In general, the potential clinical significance of drug interaction with these dihydropyridines varies inversely with their absolute bioavailability. For details, please consult relevant product monographs.

Grapefruit juice, in quantities equivalent to a normal breakfast glassful, effectively inhibits the isoenzyme CYP 3A4 up to at least 24 hours after ingestion. Therefore, it is prudent to avoid the ingestion of grapefruit juice or grapefruit when a dihydropyridine is being taken.<2>

The Ad Hoc EAC also recommended that thorough monitoring and data evaluation be conducted for bleeding episodes in all ongoing and future clinical trials in patients treated with CCBs, because preliminary evidence exists that indicates a possible association. In order to allow us to evaluate this potential adverse drug reaction more fully, we welcome and encourage you to provide us with reports of any suspected drug reactions with CCBs, including those associated with bleeding.

References

1. Grossman E, Messerli F, Grodzicki T, Kowey P. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? *JAMA* 1996;276:1328-31.
2. Bailey DG, Arnold MO, Spence JD. Grapefruit juice and drugs. How significant is the interaction? *Clin Pharmacokinet* 1994;26(2):91-8.

This article is under the direction of: Guy Beaulieu, PhD, Mick Gelsema, PhD, and Ken Gruchalla, MD

Severe iatrogenic hepatitis associated with azithromycin

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) reviewed 2 reports of severe iatrogenic hepatitis in patients on azithromycin. Both patients received 500 mg as a single dose on the first day followed by 250 mg once daily for 4 subsequent days.

The first patient, a 45-year-old man, was diagnosed with severe iatrogenic toxic hepatitis. The patient had been given azithromycin for an episode of acute bronchitis; he had not been

taking any concomitant drugs. No other medical problems were reported. Within 7 weeks after beginning the course of azithromycin, malaise, anorexia, fatigue, myalgia and nausea had developed, followed by fever and jaundice. On admission to hospital, he was icteric. The results of antinuclear antibody test and the serology tests for hepatitis A, B and C were negative. His liver enzyme levels were elevated as follows: ALT 1091 U/L (normal range 0-35), AST 1750 U/L (normal range 0-35) and alkaline phosphatase 232 U/L (normal range 30-120). His bilirubin level was 565 μmol/L (normal range 2-18). Liver biopsy was consistent with a massive necrosis (mostly centrolobular), infiltrated and enlarged portal tracts with numerous eosinophils and mononuclear elements. He subsequently underwent a liver transplantation 78 days after completing his treatment with azithromycin and was recovering at the time of reporting.

The second patient, an 85-year-old man with a history of 3 myocardial infarctions in the last 5 years, atrial fibrillation, ulcers, urinary problems and asthma, was treated for bronchitis with azithromycin. Within 6 weeks after beginning azithromycin he became ill and was hospitalized because of acute hepatitis. He was on 12 concomitant drugs including acetylsalicylic acid, enalapril, furosemide, glyburide, lovastatin, omeprazole and terazosin. Some of these drugs have the potential to cause liver injury. Liver biopsy showed hepatocellular damage compatible with a drug reaction, and his bilirubin level was greater than 300 μmol/L. When he started his treatment with azithromycin, 52 days before his death, there was no indication of liver dysfunction.

Results from controlled clinical trials reveal that the overall incidence of adverse events associated with azithromycin is about 12%.<1> The current product monograph indicates that increased liver enzyme values are potential side effects in patients receiving azithromycin. Rare but potentially serious side effects, including cholestatic jaundice, have occurred. The monograph also states that drug-induced hepatitis and hepatic necrosis "have been reported in patients under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain or in patients treated with significantly higher than the recommended doses for prolonged periods."

The first case reminds health professionals that azithromycin therapy has the potential to be associated with centrolobular necrosis in patients with no history of liver disease. These 2 cases also emphasize the need for awareness of serious hepatotoxic effects and to ensure that the prescribing of azithromycin should be undertaken with caution in patients with significant hepatic disease.

Reference

1. Charles L, Segreti J. Choosing the right macrolide antibiotic. *Drugs* 1997;53(3):349-57.

This article is under the direction of: Pascale Springuel, BPharm

Satisfaction with the Canadian ADR Newsletter — survey results

A questionnaire (English and French) was included in the October 1996 issue of the Canadian Adverse Drug Reaction Newsletter, with a view to evaluating the newsletter's usefulness and obtaining suggestions for improvement. The distribution occurred over a period of approximately 5 to 6 months because of the mailing schedules of the various pharmacist licensing authorities.

The survey contained questions on the content of the newsletter, relevance to practice, satisfaction with the type of information, satisfaction with the mailing schedule and means of distribution, as well as demographic data. Questions were either of the Yes/No type or based on a 4-point Likert scale anchored with levels of interest between None and High. There also were opportunities to make comments.

Analysis

Data capture was done using the software Epi Info (Centers for Disease Control and Prevention, Atlanta), and statistical analyses were done using SAS software (SAS Institute, Cary, NC). For ease of interpretation the 4-point Likert scale was divided into 2 categories (High and Moderate v. Low, None and Other).

Results

A total of 410 completed questionnaires were returned by April 1997. There were responses from 325 pharmacists, 66 physicians, 1 dentist, 5 nurses and 13 nonspecified respondents. One hundred and eight respondents practised in an institution, and 221 practised in the community.

Over 90% of the respondents considered the newsletter relevant to their practice, its distribution satisfactory and its length adequate (99.8%, 93.9% and 90.0% respectively). About 70% did not want a change in the quarterly distribution. Of the 108 who did suggest a change, 96% were pharmacists. About 46% suggested a monthly newsletter, and about 42% every second month.

When asked about interest in content, more than 90% indicated the following ADR topics: for new drugs (less than 5 years on the market), for older drugs, for individual drugs, and for a class of drugs. For these topics, the proportion of respondents did not differ much between the 3 main groups (pharmacists, physicians and others) except for ADRs for a class of drugs, which was chosen by 5% more pharmacists than physicians. The highest rate of interest was for ADRs for new drugs (98.1%).

Some topics received mid-level interest scores (overall 70% to 89%). These were: articles on specific reactions, ADR profiles, list of Drugs of Current Interest, changes in labelling of ADRs in product monographs, specific topics (e.g., switch to over-the-counter status), and an annual index. When compared with the

previous topics (of interest to 90% or more of the respondents) the difference in proportions between the groups was larger, with more pharmacists than physicians indicating interest. The largest difference (75.1% v. 54.6%) was found for an annual index.

The least popular topics (chosen by less than 70% overall) were for: information on international safety issues, insertion of an ADR reporting form in the newsletter and editorials on the CADRMP.

Discussion

Results must be interpreted with caution because of the small number of respondents. The survey was included in an issue of the newsletter, and there was no individual follow-up, but only a brief reminder in the Jan. 1, 1997, issue.

The response rate may have been affected by the means of distribution. Because the newsletter is sent as an insert in a professional journal, or is included in information mailed out by the provincial licensing body or professional associations of pharmacists, the motivation to respond to the questionnaire may be less than if the questionnaire had been mailed separately. Nevertheless, the results provide valuable information. Most of the respondents were pharmacists. Accordingly, interpretation of this data is swayed by this particular group. It may also mean that pharmacists have more interest in receiving information on ADRs than other health care professionals.

Approximately one-quarter of the respondents provided written comments. Several compliments on the articles were made; the newsletter was described as a useful tool that provided important, relevant information on ADRs. There were suggestions for an index, more timely distribution and direct mailing.

In conclusion, the survey results showed that the main interest is in ADRs for new drugs. Quarterly distribution is satisfactory, although means of distribution could be improved.

The results will be used with other information being collected, to plan and implement further changes.

Prepared by Carole Bouchard, BPharm, Frances Laffey, MSc, and Wikke Walop, PhD. The contribution by Patricia Leblanc is greatly appreciated.

Communiqué

The purpose of this new section is to increase awareness of recently reported ADRs. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the product monograph. They are intended to prompt reporting.

Protease inhibitors

The Therapeutic Products Programme (TPP) is aware of approximately 152 cases worldwide of *new or exacerbated diabetes mellitus and hyperglycemia* in HIV-infected patients receiving protease inhibitors. The Canadian reports received include 6 for Crixivan® (indinavir sulfate) and 2 for Invirase™ (saquinavir mesylate). Three patients recovered from hyperglycemia, 1 started insulin therapy, but hyperglycemia persisted, 1 died from sepsis, and 3 cases were of unknown outcome. In 4 of these 8 cases, the patients were known to have diabetes. However, there is no conclusive evidence to establish a causal relationship between protease inhibitor therapy and these events. Health Canada will be monitoring the situation closely as further information becomes available. An information sheet has been issued by the TPP in this regard.<1>

Vigabatrin (Sabril®)

A number of reports of ophthalmological abnormalities including *visual field constriction, bilateral optic disc pallor, subtle peripheral retinal atrophy and optic atrophy* associated with the use of vigabatrin have been collected from various countries by Hoechst Marion Roussel in the course of international postmarketing surveillance.<2>

Terconazole (Terazol™ 3 vaginal ovules/cream)

A 25-year-old woman gradually developed *erythema multiforme* covering 90% of her body surface a few days after intravaginal administration of terconazole ovules and suspected topical administration of terconazole vaginal cream. The situation progressed to *Stevens-Johnson syndrome and toxic epidermal necrolysis* within 24 hours. Sepsis developed, and the patient died from severe complications following acute renal failure and subsequent cardiac arrest. Concomitant medication use included the contraceptive Ortho® 1/35. The patient had used a *Lactobacillus* herbal preparation 4 to 5 days before using the terconazole.

Fen-phen (a combination of fenfluramine and phentermine)

The TPP has been informed that *33 cases of cardiac valvulopathy* have been reported to the US Food and Drug Administration following the use of fen-phen. In Canada, 1 case or possibly 2 cases of adverse cardiac events were reported to the CADRMP. Although the drugs (Ponderal® and Pondimin® [fenfluramine], Fastin® and Ionamin® [phentermine] as well as Tenuate® [diethylpropion]) have been approved for use as *individual* agents for short-term use (no longer than 3 months) in the management of obesity, their concomitant use has not been approved either in

Canada or in the US. However, it is known that physicians may prescribe these products in combination. There is no definitive causal relationship that has yet been confirmed between valvular heart disease and the combined use of these products; however, the trend is considered to be serious enough to warrant early intervention. Accordingly, the TPP has issued an information sheet<3,4> advising physicians against prescribing any combination of anti-obesity drugs until further information becomes available.

***New developments have arisen since submitting the Newsletter for printing. Please refer to Health Canada's Warning letter dated September 15, 1997, *Warning not to use products containing fenfluramine (Ponderal, Pondimin) or dexfenfluramine (Redux)*, for updated information.**
Public Inquiries: (613) 957-2991

Heparin

A cluster of reports of *retroperitoneal bleeding* associated with the use of heparin products has been received. Hemorrhage is the main adverse effect of heparin therapy. This risk may be increased in certain patients, such as the elderly and those taking medication affecting the clotting cascade. The package insert should be consulted for instructions regarding proper use of heparin, including monitoring of coagulation parameters and the adjustment of dosages as required. *Different assay methods exist for measuring and expressing the potency of heparin products. The 2 major units are USP Units and International Units. However, they are not equivalent<5> and thus cannot be used interchangeably at equivalent doses.*

Paroxetine (Paxil®)

A 13-month-old boy with prenatal exposure to paroxetine exhibited *delayed global development*. No other drugs had been taken by the mother; as well, no other obvious causative factors were identified.

A female infant born at 35 weeks' gestation had *intraventricular and subarachnoid bleeding*. The mother had been taking paroxetine from the 16th week of pregnancy until delivery. The baby recovered from the bleeding, but according to the physician permanent neurological damage may occur.

A 29-year-old woman, while taking paroxetine, experienced a *miscarriage* during the first trimester of pregnancy (at 8 weeks). No other drugs were taken concomitantly.

References

1. *Reports of diabetes and hyperglycemia in patients receiving protease inhibitors for the treatment of human immunodeficiency virus (HIV)*. Ottawa: Therapeutic Products Programme; 1997 July 4.

2. *Important Health Canada safety information* [letter]. Laval (QC): Hoechst Marion Roussel Canada; 1997 June 27.
3. Heart-valve disease linked to common diet drug. *Can Med Assoc J* 1997;157:362.
4. *Cardiac adverse reactions in patients following the use of fen-phen (a combination of fenfluramine and phentermine)*. Ottawa: Therapeutic Products Programme, 1997 July 11.
5. Reynolds JEF, editor. *Martindale. The extra pharmacopeia* (electronic version). Englewood (CO): Micromedex, Inc; 1995.

This section is under the direction of: Amal Hélal, BSc Phm, in collaboration with Cathy Parker, BSc, Pascale Springuel, BPharm, and Ann Sztuke-Fournier, BPharm

If you have observed similar cases, *please report* to the ADR Reporting Unit, Continuing Assessment Division, Bureau of Drug Surveillance, AL 4103B1 Ottawa ON K1A 1B9; fax 613 957-0335; or to a participating regional centre. (Check the *CPS* Clin-Info section on ADR reporting for complete addresses and to obtain a copy of the reporting form.)

This newsletter can be found on line, under Publications, at the following *new* address:

www.hc-sc.gc.ca/hpb-dgps/therapeut

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